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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/506,011	02/17/00	COX J	017227/0155

HM12/0523

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EXAMINER	
FOLEY,S	
ART UNIT	**PAPER NUMBER**
1648	11

DATE MAILED: 05/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/506,011	Applicant(s) COX ET AL.	
	Examiner Shanon A. Foley	Art Unit 1648	

-- The MAILING DATE of this communication appears on th c ver sh et with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-43 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Pap r No(s) 9 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *Notice to Comply* .

DETAILED ACTION

Inventorship

In view of the papers filed March 13, 2001, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by addition of Andreas Suhrbier.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Sequence Requirement

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-43 and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 and 35-47 of copending Application No. 09/714438. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application claims a charged antigen and a negatively charged adjuvant. The adjuvants in both applications consist of identical ingredients. The pathogens of interest in the instant application are listed in claim 43 and one of the antigens/pathogens is more distinctly defined and claimed in 09/714438. Therefore, the instant application claims a genus of pathogens treated by the charged composition, which would be obvious over the species claimed in 09/714438.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 16 and 33, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-43 and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 18-43 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for peptides HpC, SYI, YPH, or RPQ with 6 lysines (K) and 6 histidines (H) associated with cardiolipin (CDL) or diphosphoryl lipid A (DPL), or CHL, does not reasonably provide enablement for any positively charged protein and any negatively charged adjuvant to prevent, inhibit, halt, or delay the onset or progression of any microbial pathogen or cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn a vaccine composition comprising a positively charged antigen and a negatively charged adjuvant to induce a cytotoxic immune response to treat or prevent any disease or cancer. It has not been demonstrated that every positively charged antigen can reasonably be expected to induce a CTL response when combined with any negatively charged

adjuvant. The examples in the specification mainly focus on the association of the antigen with various adjuvants and standard optimization techniques to improve the association. Specifically, peptides HpC, SYI, YPH, or RPQ with 6 lysines (K) and 6 histidines (H) associated with cardiolipin (CDL) or diphosphoryl lipid A (DPL), or CHL demonstrate induction of a cytotoxic T cell response and the most successful pairing occurred when a positive antigen was associated with CDL or DPL, see examples 2-7. However, combinations that were administered to mice in examples 4 and 6 did not state which ISCOMATRIX™ was used to get a positive response. In addition, while the specification teaches that mice had a CTL response in examples 4, 6, 9, 14, and 17, there is no indication that the response was directed to the antigen specifically or to the particular ISCOMATRIX™ used to boost the response to the antigen. The mice were never challenged with any pathogen directly after immunization to test for efficacy or to examine how long the antigen/adjuvant remained *in vivo*. The specification does not demonstrate that there is any predictability with how well proteins will associate because even though TYQ in example 17 was treated to increase positivity by the addition of 6H and 6K, and associated with a negatively charged adjuvant, CHL, very weak responses to this epitope were generated.

The teachings of Barr et al. are used to demonstrate the state of the art of ISCOM™ technology at the time the invention was made. Barr et al. teaches that some ISCOM™ short-comings involve inconsistency in the performance of adjuvants with different antigens, see the second column on page 8. The reference also teaches that hydrophobic transmembrane sequence incorporated onto a peptide is insufficient to guarantee the insertion of molecules into ISCOMs™, see the first paragraph under "ISCOMs containing..."on page 11. Also, the small size of ISCOMs™ is a limiting factor in the incorporation of large molecules, see the first

paragraph under "ISCOMs containing..."on page 12. In addition, there is a lack of data demonstrating that ISCOM™-delivered antigens induce long-term immunological memory, see the past section of the first column on page 20.

Offringa et al. teaches a vaccine strategy against cancer that involves the use of peptides that had been emulsified in adjuvants that were able to induce protective anti-tumor immunity in several murine models. However, on closer inspection, these formulations were not always sufficient for true anti-tumor immunity and in some cases, the vaccines were even found to cause T cell tolerance instead of immunity. See the abstract.

Therefore, based on the enormous scope of the claims, the preventative nature of the invention toward all diseases, the lack of guidance provided by the inventor that would lead the skilled artisan to a protective effect with any combination of protein and ISCOM™ adjuvant, the lack of working examples demonstrating a protective immune response, the unpredictability for these combinations in the art, it is determined that undue experimentation would be required of the skilled artisan to make or use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Seeber et al.

The claims are drawn to a negatively charged adjuvant and a positively charged antigen.

Seeber et al. teaches that electrostatic attraction has a major role in adsorption and demonstrates two proteins and their ability to adsorb different proteins with isoelectric points. One of the examples is amorphous aluminum hydroxyphosphate, which has a point of zero charge at 4.0, effectively adsorbing lysozyme, which has an isoelectric point at 11.0, see the abstract. These teachings clearly anticipate claims 1-5.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Al-Shakhshir et al.

Al-Shakhshir et al. teaches that a positively charged lysozyme and a negatively charged aluminum phosphate adjuvant resulted in the increase in the point of zero charge and was concluded that physiochemical properties of the antigen-adjuvant complex should be considered during vaccine preparation due to physiological pH adsorption rate of the positively charged antigen by the adjuvant, see the abstract and the results and discussion section.

Claim Rejections - 35 USC § 102

Claim Rejections - 35 USC § 103

Claims 1-8 and 12-14 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nakanishi et al.

The claims are drawn to an immunogenic complex comprising a positively charged antigen and a negatively charged adjuvant that are electrostatically associated. The degree of each of the charges has been enhanced. The negatively charged adjuvant comprises a phospholipid, such as phosphatidic acid (PA).

Nakanishi et al. teaches immunogenic complexes of multilamellar vesicles (MLV) with positive, negative, and neutral charges, see Table 1 and the materials and methods section. The

vesicles all contain phosphatidylcholine and have been enhanced to become more negatively charged by the addition of phophatidic acid. These MLVs were assayed to determine the cytotoxic response, see figure 2. Nakanishi et al. does not explicitly teach that the antigens have a positive charge and are electrostatically associated with the negatively charged vesicle. However, the reference teaches that the negatively charged vesicles are composed of an amphipathic molecule, phosphatidylcholine. The negatively charged end of this molecule would be found in the interior of the vesicle, which associates directly with the protein antigen. Since some amino acids inherently have a positive charge, and these amino acids would be naturally attracted to the negative charge of the phosphatidylcholine, creating an electrostatic association between the antigen and the vesicle in some degree. Therefore, the teachings of Nakanishi et al. are obvious, if not anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seeber et al. or Al-Shakhshir et al.

The claims are drawn to enhancing the degree of positive charge of an antigen and the degree of negative charge of the adjuvant.

See the teachings of Seeber et al. or Al-Shakhshir et al. above. Neither reference teaches enhancing the degree of charge for either antigen or adjuvant. However, it would have

been an obvious modification for one of ordinary skill in the art at the time the invention was made to optimize the degree of charge for either or both adjuvant and antigen. Modification would have been necessary due to the particular natural characteristics of the antigen or adjuvant of interest and the desired effect of adsorption and/or the electrophoretic mobility of specific complexes *in vivo*. In addition, Al-Shakhshir et al. teaches that cysteine and histidine will ionize at a pH range between 5 and 9 and gives the characteristic pKa values in some amino acids, see table 1. This teaching would enable one skilled in the art at the time the invention was made to analyse the amino acid content in reference to the pKa values and readily determine how a specific protein will react at the desired physiological pH, and add or subtract particularly charged amino acid species as required.

Claims 9-11 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakanishi et al. as applied to claims 1-8, 12-14 above, and further in view of Barr et al.

See the teachings of Nakanishi et al. above. Nakanishi et al. does not expressly teach the use of ISCOMATRIX™ or saponin complexes. However, Barr et al. reviews different ISCOMs, and names saponin, lipid A, and phospholipids (taught by Nakanishi et al.) as obvious variants to one another. In addition, Therefore, it would have been obvious for one of ordinary skill in the art to substitute equivalents based on what most available at the time.

Claims 18-43 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seeber et al. or Al-Shakhshir et al., and Nakanishi et al. as applied to claims 1-17 above, and further in view of Barr et al.

See the teachings of Seeber et al. or Al-Shakhshir et al. above. Seeber et al. or Al-Shakhshir et al. teach the importance of positive antigen and negative adjuvant association in

vaccine compositions. Neither reference teaches the use of ISCOM™ or phospholipids in vaccine compositions, or a method of enhancing the negative charge of the adjuvant of choice. However, Nakanishi et al. teaches a method of enhancing the negative effect of a phospholipid with the addition of phosphatidic acid. It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase the negative charge of the adjuvant taught by Nakanishi et al. in order to increase the adjuvant's ability to adsorb different proteins with isoelectric points, taught by Seeber et al. and optimize the physiochemical properties of the antigen-adjuvant complex taught by Al-Shakhshir et al. As discussed above, Barr et al. reviews different ISCOMs, and names saponin, lipid A, and phospholipids, taught by Nakanishi et al., as obvious variants to one another. In addition, Barr et al. teaches that incorporation of antigens, see Table 3 on page 16, into ISCOMs™ stimulate CTL responses *in vivo*. See "immune modulation" on pages 14-15, also see Table 3 in reference to the various protection observed with specific antigens. Therefore, based on the strong immune responses observed in antigens incorporated by ISCOMs™ taught by Barr et al., the method of increasing the negative charge of a particular ISCOM™ taught by Nakanishi et al., and the motivation for optimizing antigen/adjuvant association in a vaccine composition, taught by Seeber et al. and Al-Shakhshir et al., it is determined that the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate successful immunogenic compositions into similar compositions in a vaccine.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 7:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
May 18, 2001

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

Application No.: 09506011

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:
For Rules Interpretation, call (703) 308-4216
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